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CLINICAL TRIAL PAPER

Resting respiratory variables and exercise capacity in adult patients with cystic fibrosis

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KEYWORDS
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Summary
Introduction: Cystic fibrosis (CF) is the most common life-limiting, recessively inherited disease in the white population, associated with significantly high morbidity and mortality rates; CF pulmonary disease, assessed by pulmonary function tests, arterial blood gases and the Schwachman score, remains the most prevalent in terms of morbidity in the adult CF population.
Objectives: The aim of the present study was to evaluate the relationship between resting respiratory variables and exercise capacity in adult patients with CF.
Results: Study investigations undertaken in 18 CF patients and 11 healthy volunteers showed that among the resting lung function parameters, inspiratory capacity (IC) at rest was the only significant predictor of VO_2 peak ($r = 0.67$, $p < 0.007$) and VO_2/t-slope ($r = 0.86$, $p < 0.0001$). The percentage of predicted FEV_1 in adult CF patients was $77 \pm 33\%$ pred. vs $104 \pm 16\%$ pred. in healthy subjects ($p < 0.006$); the corresponding percentage of IC at rest was $82 \pm 36\%$ pred. in patients vs $116 \pm 20\%$ pred. in healthy ($p < 0.003$). CF patients presented with a significantly prolonged rapid breathing after exercise (32br per minute at recovery for CF vs 22 for healthy; $p < 0.001$), as well as a shortened inspiratory time.
Conclusion: Adult patients with CF show a limited exercise capacity with lower peak oxygen consumption and prolonged oxygen kinetics. Interestingly, decreased IC qualified as the only significant predictor of exercise capacity in our study.

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Introduction

Cystic fibrosis (CF) is a progressive, life-limiting disease with an autosomal recessive pattern of inheritance and a significantly high incidence of 1:2000 to 1:3500 among Caucasian populations.[1,2] The advances in the therapeutic management of CF over the years gradually led to a significant increase in life expectancy, accompanied by a corresponding increase in the rate of CF patients surviving into adulthood.[3,4] Following the chronicity of the disease, CF patients present a continuously increasing morbidity, with the respiratory system being the most commonly affected among the adult population.[5,6] Indeed, the progressive decline in lung function is considered to be the major determinant of survival.[7] Mucus plugging of small airways, followed by bacterial infection causes chronic inflammatory damage. Early radiological changes include hyperinflation and areas of atelectasis along with bronchiectasis in the later stages of disease.[8] As disease progresses, there is flow limitation in large as well as small airways. In terminal CF lung disease severe airway obstruction is the rule.[9–12] Tidal expiratory flow limitation (EFL) has been associated with chronic dynamic hyperinflation during tidal breathing[13] where end-expiratory lung volume is grater than the relaxation volume of the respiratory system. Furthermore it is known that EFL promotes dynamic hyperinflation during exercise in COPD patients with a consequent reduction in Inspiratory Capacity (IC), limiting their exercise tolerance.[14–16] Therefore, the exercise capacity of patients with tidal EFL at rest should depend on the magnitude of IC. CF pulmonary disease is assessed by pulmonary function tests, arterial blood gases and Schwachman score (SS).[17] SS is a scoring system based on general activity, physical findings, nutritional status and chest radiography (Table 4). Patients with end-stage pulmonary disease are considered as potential candidates for lung transplantation. $FEV_1 \leq 30\%$, $PaCO_2 > 50$ mmHg and $PaO_2 < 55$ mmHg are indications for lung transplantation[18] while VO_2 max $< 56\%$ pred., poor 6 min walk performance, pulmonary hypertension and body mass index (BMI) $<$ 18 kg/m^2 are additional considerations correlated with worse prognosis. Maximal exercise capacity in CF is reduced. Oxygen consumption during maximal exercise (VO_2 peak) serves as a valuable monitoring tool for the assessment of cardiorespiratory fitness level. Reduced exercise ability correlates with prolonged oxygen kinetics during maximal exercise and early recovery.[19–21] The aim of the present study was to investigate the relationship between resting respiratory variables and exercise capacity in adult patients with CF.

Table 1 Baseline characteristics of the 18 CF and 11 healthy subjects.

	Patients with CF $N = 18$ $x \pm sd$	Healthy subjects $N = 11$ $x \pm sd$
Gender (M/F)	9/9	3/8
Age (years)	21 ± 11	29 ± 4
Schwachman score	74 ± 11	–
BMI (body mass index)	19 ± 3	24 ± 3
FEV_1 (% pred.)	77 ± 33	104 ± 16
FVC (% pred.)	95 ± 30	106 ± 15
FEV_1/FVC (% pred.)	69 ± 16	86 ± 6
IC (ml)	2273 ± 1010	2858 ± 546
IC (% pred.)	82 ± 36	116 ± 20

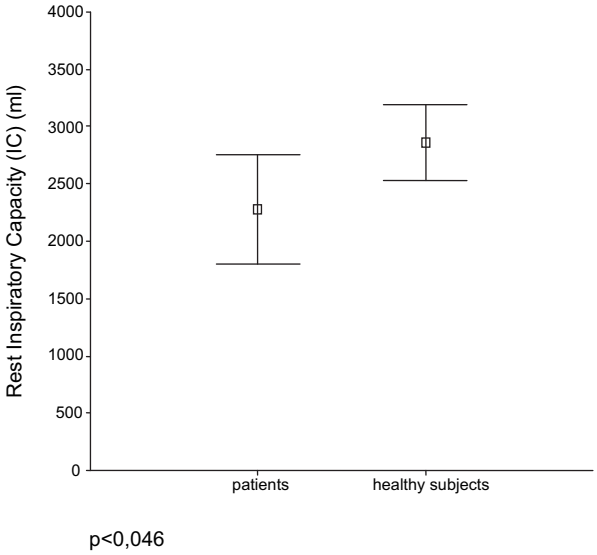

Figure 1 Rest inspiratory capacity (mean $\pm$ SE) in adult patients with cystic fibrosis and healthy subjects.

Patients and methods

Patient population

18 patients with CF (9 male/9 female, aged 21 ± 11y) and 11 healthy subjects (3 male/8 female, aged 29 ± 4y) were

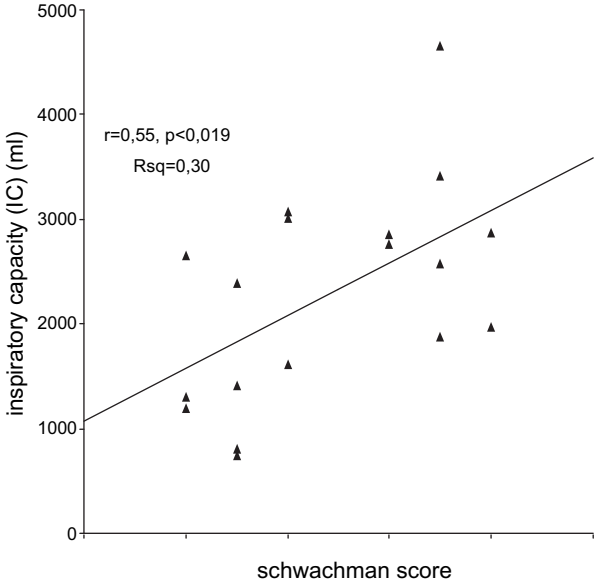

Figure 2 Scatter graph of IC vs Schwachman score in adult patients with cystic fibrosis.

Table 2 CPET indices at rest, peak exercise and recovery for both groups.

	Patients			Healthy subjects		
	Rest	Peak	Recovery	Rest	Peak	Recovery
V_E (lt/min)	12.5 ± 2.4	57.2 ± 19	14.4 ± 6.7	11.3 ± 2	81.3 ± 13.2	20.5 ± 5.8
V_T (lt)	0.56 ± 0.1	1.53 ± 0.6	0.72 ± 0.3	0.57 ± 0.2	1.88 ± 0.4	1.2 ± 0.3
f_b (breaths/min)	23 ± 6	38 ± 9	32 ± 8	19 ± 4	44 ± 8	22 ± 5
T_I (s)	1.2 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	1.5 ± 0.3	0.7 ± 0.1	1 ± 0.2
V_T/T_I (lt/s)	0.5 ± 0.2	1.9 ± 0.6	0.8 ± 0.3	0.4 ± 0.1	2.7 ± 0.4	1.2 ± 0.3
VO_2	4.93 ± 1.8	29.12 ± 7	5.77 ± 3.3	4.03 ± 1.1	35.54 ± 7.3	4.82 ± 1.9
V_D/V_T	0.35 ± 0.2	0.16 ± 0.02	0.19 ± 0.04	0.36 ± 0.2	0.10 ± 0.02	0.16 ± 0.04
V_E/VO_2		25.65 ± 5.5			19.9 ± 5.88	
V_E/VCO_2		28.51 ± 5.3			26.62 ± 3.14	
VO_2/t-slope		0.59 ± 0.25			0.95 ± 0.18	

investigated. Anthropometric, clinical and resting pulmonary function characteristics of both groups are listed in Table 1. Both patients and healthy subjects underwent pulmonary function test at rest and symptom-limited treadmill cardiopulmonary exercise testing (CPET).

Pulmonary function tests

Measurements of FVC and FEV_1 were obtained in the sitting position using a closed-circuit spirometer (Vmax model 229; SensorMedics; Yorba Linda, CA), as recommended by the American Thoracic Society.[22]

Inspiratory capacity measurement

The procedure of inspiratory capacity (IC) measurement was explained in detail to all participating subjects. Patients were instructed to breathe normally, in the sitting position, through a mouthpiece connected to a calibrated pneumotachograph. Upon the achievement of steady tidal volume (V_T) and end-expiratory lung volume, a maximum inspiration to total lung capacity (TLC) was performed. This procedure was repeated four times. In all instances, subjects performed at least three satisfactory maneuvers, two of which did not differ by >5%. The best IC was selected. This approach has been previously demonstrated to be reliable and reproducible.[23]

CPET

Each subject underwent a symptom-limited, incremental CPET on a treadmill (Marquette Electronics 2000; Marquette Electronics; Milwaukee, WI) on the same day as the pulmonary function tests, utilizing the modified Naughton protocol.[24] All parameters were recorded in the upright position before and during exercise and in the sitting position for the first 10 min of recovery. A 12-lead ECG was recorded every minute using the MAX 1 system. Blood pressure (BP) measurements were obtained every 2 min using a standard cuff-mercury sphygmomanometer. A pulse oximeter was used for the monitoring of pulse oximetric saturation. Baseline VO_2 was calculated by averaging the measurements obtained for 2 min before the onset of exercise. VO_2 peak was calculated as the average of measurements obtained over the 20 s before the

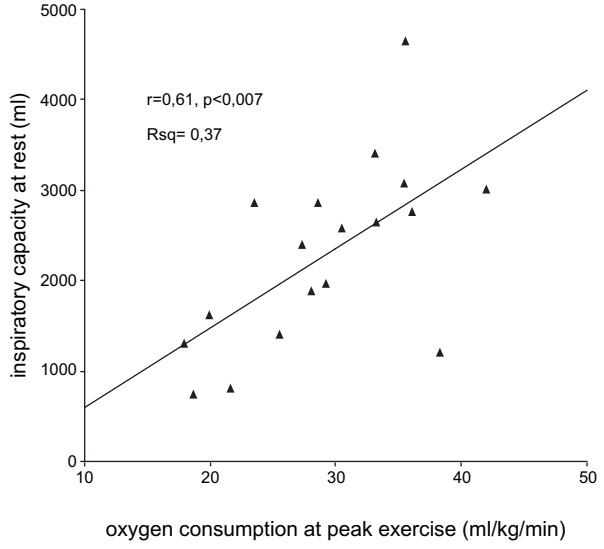

Figure 3 Scatter graph of IC at rest vs VO_2 peak in adult patients with cystic fibrosis.

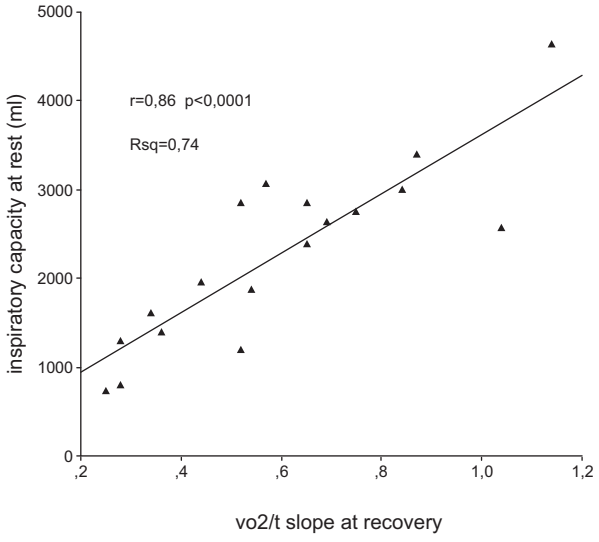

Figure 4 Scatter graph of IC at rest vs VO_2/t-slope in adult patients with cystic fibrosis.

termination of the exercise. Anaerobic threshold was determined using the V-slope technique[16] and the result was confirmed by a graph on which respiratory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2) were plotted simultaneously against time. In order to evaluate the oxygen consumption kinetics during recovery, the first degree slope of VO_2 for the first minute of recovery period (VO_2/t-slope) was calculated by linear regression using an appropriate computerized statistical program.[25] Patients were encouraged to exercise scoring their sense of exhaustion, leg fatigue and dyspnea using Borg scale.

Statistical analysis

Results are presented as means ± standard deviation (SD). The unpaired Student's t-test was used for the comparison of CF patients against healthy subjects at rest. Analysis of variance for repeated measures was used to compare changes in CPET indices within and between subjects. Correlations were tested by Pearson's correlation coefficient. A multivariate linear regression analysis was used to test the independent association of lung function with oxygen kinetics (VO_2 peak and VO_2/t-slope), followed by a stepwise regression analysis. A p value <0.05 was considered statistically significant.

Results

Resting pulmonary function data are presented in Table 1. FEV_1 in patients was 77 ± 33% pred vs 104 ± 16% pred in healthy subjects ($p < 0.006$) and IC at rest was 82 ± 36% pred in patients vs 116 ± 20% pred in healthy ($p < 0.003$) or 2273 ml ± 1010 in patients vs 2857 ml ± 545 in healthy ($p < 0.046$) (Fig. 1). IC was correlated with Schwachman score (SS): $r = 0.55$; $p < 0.019$; (Fig. 2). CPET indices at rest, peak exercise and recovery for each group are presented in Table 2.

Patients' ability to increase V_T and V_E was limited in comparison with healthy subjects (from 0.56 to 1.53 lt vs 0.57 to 1.88 lt, $p < 0.013$ and 12.57 to 57.2 lt/min vs 11.3 to 81.3 lt/min, $p < 0.001$ respectively). CF patients showed similar ability to increase breathing frequency from rest to exercise in comparison with healthy subjects (23br per minute to 38 vs 19 to 44; $p < 0.098$), however they exhibited a prolonged rapid breathing after exercise (32br per minute at recovery for CF patients vs 22 for healthy subjects; $p < 0.001$) along with shortened inspiratory time.

Mean peak oxygen uptake (VO_2 peak) was 29.12 ± 7.02 ml/kg/min in patients vs 35.54 ± 7.31 in healthy subjects; ($p < 0.01$) while VO_2/t-slope at early recovery was 0.59 ± 0.25 in patients vs 0.95 ± 0.18 in healthy ($p < 0.0001$).

In a multivariate stepwise regression analysis, using peak VO_2 as the dependent variable and the pulmonary function test measurements as independent variables respectively, the only significant predictor emerged was IC ($r = 0.608$; $p < 0.007$). VO_2/t-slope was also lower in CF patients (0.59 ± 0.25 vs 0.95 ± 0.18; $p < 0.0001$) and showed significant correlation with IC ($r = 0.859$; $p < 0.0001$). In a final stepwise regression analysis including all independent variables of the resting pulmonary function tests, the only predictor selected for VO_2 peak and VO_2/t-slope was IC ($r^2 = 0.37$ for VO_2 peak and 0.74 for VO_2/t-slope) (Figs. 3 and 4).

The significant correlations of VO_2 peak and VO_2/t-slope to resting lung function are listed in Table 3.

Discussion

Only a few trials have been performed to evaluate some exercise variables in adult patients with cystic fibrosis. The first time that exercise limitation in CF patients had been correlated with pulmonary mechanics rather than circulatory factors and hypoxia was in 1971 (Godfrey et al).[26] In 1990 Browning and coworkers investigating 11 adult patients with CF showed that there was a correlation between disease severity and respiratory rate during exercise.[27] Lands et al. (1992) in a study with 14 patients found V_E max and VO_2 max decreased during exercise without V_E/VO_2 and V_E/VCO_2 difference between patients and healthy controls.[28] In the same study VO_2 max correlated with FEV_1. Nixon (1992) and Webb (1997) confirmed that VO_2 max was statistically significant prognostic index for disease severity and survival.[29,30] Pouliou et al. (2001) describe dprolonged oxygen kinetics at early recovery in adult patients with CF.[20] The above mentioned trials concluded exercise limitation in CF patients.

The main finding of this study indicates that in patients with CF, IC at rest represents the only significant predictor of VO_2 peak and VO_2/t-slope among the resting lung function parameters, according to multivariate stepwise regression analysis. The decrease of IC observed in our study was related to disease's severity. Our results revealed prolonged VO_2 kinetics during early recovery. Both VO_2/t-slope and VO_2 peak values were significantly lower in CF patients in comparison with those of healthy subjects.

Furthermore, ventilatory response during exercise, including a lot of parameters, is described, which was altered at different stages of exercise. In CF patients there is a limitation in ability to increase V_E due to their lower V_T.

Table 3 Significant correlations of VO_2 peak and VO_2/t-slope to various resting respiratory parameters.

Parameters	VO_2 peak		VO_2/t-slope	
	r	p value	r	p value
FEV_1, % pred	0.575	0.013	0.774	0.0001
FVC, % pred	0.602	0.008	0.663	0.003
FEV_1/FVC, %	0.513	0.029	0.678	0.002
IC, ml	0.608	0.007	0.859	0.0001

Table 4 Schwachman–Kulczycki score.

Points	General activity	Physical examination	Nutrition	X-ray findings
25	Full normal activity. Plays ball, goes to school regularly.	No cough, clear lungs, normal HR & RR, good posture.	Weight and height above 25th centile, Normal stool, good muscle mass and tone.	Normal, clear lung fields.
20	Lacks endurance, tires at end of day, good school attendance.	Rare cough, normal HR, minimal hyperinflation, clear lungs, no clubbing.	Wt and Ht 15–20th centile, stool slightly abnormal, fair muscle tone and mass.	Minimal accentuation of bronchovascular markings, early hyperinflation.
15	May rest voluntarily, tires easily after exertion, fair school attendance, tires after exertion.	Occasional cough/wheeze, increased RR, mild hyperinflation, early clubbing.	Wt and Ht above 3rd centile, stools often abnormal, large and poorly formed, minimal abdominal distension, reduced muscle mass and poor tone.	Mild hyperinflation, patchy atelectasis, increased bronchovascular markings.
10	Home teacher, dyspnoeic after short walk, rests frequently.	Frequent cough, often productive, clubbing, chest retraction, moderate hyperinflation, wheezes and crackles, moderate clubbing.	Wt and Ht below 3rd centile, bulky Offensive stool, mild to moderate Abdominal distension, flabby muscles and Reduced mass.	Moderate hyperinflation, widespread atelectasis and areas of infection. minimal bronchiectasis.
5	Orthopnoeic, stays in chair or bed.	Tachypnoea, tachycardia, severe coughing spells, extensive crackles, cyanosis, signs of heart failure, severe clubbing.	Marked malnutrition With protuberant Abdomen, rectal Prolapse, large foul Frequent fatty stools.	Severe hyperinflation, lobar atelectasis and bronchiectasis, nodules/cysts. pneumothorax, cardiac enlargement

Excellent — 86–100; Good — 71–85; Mild — 56–70; Moderate — 41–55; Severe — <40.

In their effort to increase minute ventilation, an increase in breathing frequency and shortened inspiratory time is observed. This is well depicted at recovery which is prolonged.

In CF patients there is a basic physiologic defect leading to enlarged dead space and it is present even in the most mildly affected patients. Progressive airway obstruction reduces vital capacity resulting in V_T limitation. In compensation, decreased inspiratory time and increased end-expiratory volume are observed in order to preserve adequate inspiratory and expiratory flow rates.[31,9] Airway obstruction causes prolongation of expiratory flow rate and in association with the increased breathing frequency results in air trapping.[27,32] The work and oxygen cost of breathing are increased at high lung volumes and finally exercise is discontinued.

Resting pulmonary function, VO_2 peak and VO_2/t-slope

Although FEV_1 (perc. pred.) has been reported as a good indicator of exercise capacity in CF patients,[28,30] our data suggest that IC is the only independent predictor of VO_2 peak and VO_2/t-slope among all other respiratory variables investigated. The role of IC as predictor of VO_2 peak and VO_2/t-slope has not been previously investigated in patients with cystic fibrosis.

Clinical implications

The finding that a simple, safe, non-invasive maneuver such as the measurement of IC can predict exercise capacity better than other respiratory parameters may prove to be useful in clinical settings, either when CPET is not available or when it is contraindicated.

Conclusion

In conclusion, the rest IC in adult patients with CF is the only independent predictor of peak oxygen consumption and prolonged oxygen uptake kinetics during exercise. It is easy to measure and seems to be a useful index.

Conflict of interest statement

The authors declare that no conflict of interests exists.

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